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Accumulation of 19 environmental phenolic and xenobiotic heterocyclic aromatic compounds in human adipose tissue

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ABSTRACT

The extensive use of environmental phenols (e.g., bisphenol A) and heterocyclic aromatic compounds (e.g., benzothiazole) in consumer products as well as widespread exposure of humans to these compounds have been well documented. Biomonitoring studies have used urinary measurements to assess exposures, based on the assumption that these chemicals are metabolized and eliminated in urine. Despite the fact that some of these chemicals are moderately lipophilic, the extent of their accumulation in adipose fat tissues has not been convincingly demonstrated. In this study, human adipose fat samples ($N = 20$) collected from New York City, USA, were analyzed for the presence of environmental phenols, including bisphenol A (BPA), benzophenone-3 (BP-3), triclosan (TCS), and parabens, as well as heterocyclic aromatic compounds, including benzotriazole (BTR), benzothiazole (BTH), and their derivatives. BPA and TCS were frequently detected in adipose tissues at concentrations (geometric mean [GM]: 3.95 ng/g wet wt for BPA and 7.21 ng/g wet wt for TCS) similar to or below the values reported for human urine. High concentrations of BP-3 were found in human adipose tissues (GM: 43.4; maximum: 4940 ng/g wet wt) and a positive correlation between BP-3 concentrations and donor's age was observed. The metabolite of parabens, *p*-hydroxybenzoic acid (*p*-HB), also was found at elevated levels (GM: 4160; max.: 17,400 ng/g wet wt) and a positive correlation between donor's age and sum concentration of parabens and *p*-HB were found. The GM concentrations of BTR and BTH in human adipose tissues were below 1 ng/g, although the methylated forms of BTR (i.e., TTR and XTR) and the hydrated form of BTH (i.e., 2-OH-BTH) were frequently detected in adipose samples, indicating widespread exposure to these compounds. Our results suggest that adipose tissue is an important repository for BP-3 and parabens, including *p*-HB, in the human body.

1. Introduction

Considerable concern exists with regard to human exposure to environmental phenolic chemicals due to their widespread use in consumer products and associated potential health effects. Some of the environmental phenolic compounds of concern include bisphenol A (BPA), benzophenone-3 (BP-3), triclosan (TCS), and parabens. BPA, the raw material used in the manufacture of polycarbonate plastics and epoxy resins, is a known endocrine disruptor (vom Saal et al., 2007). BP-3 is a sunscreen agent used in a variety of cosmetics to protect human skin from ultraviolet (UV) radiation and possesses both estrogenic (Dodson et al., 2012) and antiandrogenic activities (Ma et al., 2003). TCS is a synthetic, broad-spectrum antimicrobial agent used extensively in personal care and consumer products and possesses estrogenic activity (Foran et al., 2000; Ishibashi et al., 2004). The esters of *p*-hydroxybenzoic acid (i.e., parabens) are the most commonly used preservatives in foodstuffs, cosmetics, and pharmaceuticals (Soni et al., 2005; SCCS, 2011). In vitro and in vivo toxicity studies have shown the endocrine-disrupting properties of parabens (Routledge et al., 1998; Byford et al., 2002; Oishi, 2002; Boberg et al., 2010; Karpuzoglu et al., 2015; Zhang et al., 2013).

The heterocyclic aromatic derivatives of benzotriazole (BTR) and benzothiazole (BTH) (collectively referred to as BTRs and BTHs) are used in a variety of consumer products and industrial applications, and human exposure to these compounds is widespread (Asimakopoulos et al., 2013a,b; Wang et al., 2013a; Xue et al., 2015). BTRs are widely used as flame and corrosion inhibitors, UV light stabilizers in plastics, and antifogging agents (Asimakopoulos et al., 2013a,b). BTRs also are used in pigments, dishwasher detergents, dry cleaning equipment, and de-icing/anti-icing fluids (Asimakopoulos et al., 2013a,b). A few studies have reported on the toxic effects of BTR derivatives. 1H-BTR and TTR have been shown to be phytotoxic, 1H-BTR to be mutagenic to bacteria (*Salmonella*, *Escherichia coli*), and TTR to be toxic to microorganisms

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(Asimakopoulos et al., 2013b). BTHs are used as corrosion inhibitors, herbicides, slimicides (in the paper and pulp industry), algicides, fungicides (in the lumber and leather industries), and photosensitizers (Asimakopoulos et al., 2013b). In addition, the applications of BTHs in de-icing/anti-icing fluids, food flavors, and rubber production have been documented (Asimakopoulos et al., 2013b). BTH is a known constituent of tea leaves and tobacco smoke (Asimakopoulos et al., 2013b). BTH derivatives have been associated with mutagenicity in microorganisms (Kinae et al., 1981) and carcinogenicity in humans (Sorahan, 2009; Ginsberg et al., 2011).

The widespread exposure of humans to environmental phenols and heterocyclic aromatic compounds noted above is reported on the basis of the analysis of urine or blood (Ye et al., 2012; Asimakopoulos et al., 2013a,b; USCDC, 2014; Mortensen et al., 2014). However, the accumulation of these chemicals in other human body tissues has not been convincingly demonstrated. The log K_{ow} values for these chemicals are in the range of 1 to 5 (Table 1), which suggest that some of these chemicals have the ability to accumulate in fatty tissues. Nevertheless, due to the difficulty of obtaining adipose tissues (which requires invasive sampling) and the complexity of trace analysis of chemicals in lipid-rich matrices, few studies have measured heterocyclic aromatics and environmental phenols in adipose fat tissues. Occurrence of chemicals in human adipose tissue has significant implications for overall persistence, bioaccumulation, and toxicity.

In this study, concentrations of BPA, BP-3, TCS, seven parabens, five BTRs, and four BTHs were determined (for the first time for the majority of chemicals) in 20 human adipose fat tissues collected from New York City, NY, USA. The objectives of this study were to (i) determine the occurrence and profiles of target environmental phenols and heterocyclic aromatic compounds in human adipose fat tissues and (ii) examine the bioaccumulation potential of target chemicals in humans.

2. Materials and methods

2.1. Chemicals

Analytical standards of BPA, BP-3, TCS, 1-OH-BTR hydrate, 2-Me-S-BTH, and 5-Cl-1-H-BTR were purchased from Sigma-Aldrich (St. Louis, MO, USA). Methyl- (MeP), ethyl- (EtP), propyl- (PrP), butyl- (BuP), benzyl- (BzP), and heptyl-parabens (HepP) and their metabolite, *p*-hydroxybenzoic acid (*p*-HB), were purchased from AccuStandard Inc (New Haven, CT, USA). 1-H-BTR, BTH, and 2-OH-BTH were purchased from Alfa Aesar GmbH & Co KG (Karlsruhe, Germany). 5-Me-1H-BTR (TTR), 5,6-diMe-1-H-BTR (XTR) and 2-NH_2-BTH were purchased from Acros Organics (Morris Plains, NJ, USA). The molecular structures and select physicochemical properties of the target analytes are shown in Fig. S1 (Supplementary data) and Table 1, respectively. The isotope labeled internal standards, $^{13}C_{12}$-BPA (99%), $^{13}C_6$-*p*-HB (99%), $^{13}C_6$-MeP (99%), $^{13}C_6$-BuP (99%), and $^{13}C_6$-BP-3 (99%) were purchased from Cambridge Isotope Laboratories (Andover, MA, USA), whereas $^{13}C_{12}$-TCS and D_4-1-H-BTR (100%) were purchased from Wellington Laboratories Inc (Guelph, Ontario, Canada) and Sigma-Aldrich (St. Louis, MO, USA), respectively. Formic acid (98.2%) and methanol (HPLC grade) were purchased from Sigma-Aldrich and Mallinckrodt Baker (Phillipsburg, NJ, USA), respectively. Milli-Q water was prepared using an ultrapure water system (Barnstead International, Dubuque, IA, USA). The stock solutions of target analytes and internal standards were prepared at 1 mg/mL in methanol and stored at −20 °C.

2.2. Sample collection

A total of 20 human adipose samples were selected from a repository of adipose tissue samples at Wadsworth Center, which were originally collected in 2003–2004 from volunteers who underwent liposuction surgery in New York City. The samples were stored in solvent-cleaned I-Chem jars at −20 °C, as recommended by the National Human Monitoring Program (NITS, 1991). Demographic information of the volunteers is shown in Table S1, and some additional details regarding sample collection have been provided elsewhere (Johnson-Restrepo et al., 2005). Institutional Review Board approvals were obtained from the New York State Department of Health for the analysis of samples. For the evaluation of stability of target compounds in adipose tissue, an experiment was conducted by spiking target chemicals on a lipid matrix (oil) and storing them at −20 °C for 4 months. No significant loss was found for any of the target compounds (maximum loss was ~10%, for heptylparaben) (Fig. S2).

2.3. Sample preparation

A total of 200 to 300 milligrams of adipose fat tissue were accurately weighed and spiked with 50 μL of methanol solution containing $^{13}C_{12}$-BPA, $^{13}C_6$-MeP, $^{13}C_6$-BuP, and $^{13}C_{12}$-BP-3, $^{13}C_{12}$-TCS and D_4-1-H-BTR (200 ng/mL each). The samples were then equilibrated for 30 min at room temperature, and 2 mL of acetone was added for extraction. The

Table 1
Select physicochemical properties of target chemicals.

Analyte	Systematic name	Molecular Formula	CAS	Molecular Weight	Water solubility[a]	Log K_{ow}[b]
BPA	4,4'-(2,2-Propanediyl)diphenol	$C_{15}H_{16}O_2$	80-05-7	228.29	173	3.64
BP-3	(2-Hydroxy-4-methoxyphenyl)(phenyl)methanone	$C_{14}H_{12}O_3$	131-57-7	228.24	68.6	3.52
TCS	5-Chloro-2-(2,4-dichlorophenoxy)phenol	$C_{12}H_7Cl_3O_2$	88032-08-0	289.5	4.62	4.66
MeP	Methyl 4-hydroxybenzoate	$C_8H_8O_3$	99-76-3	152.15	5980	1.96
EtP	Ethyl 4-hydroxybenzoate	$C_9H_{10}O_3$	120-47-8	166.17	1890	2.49
PrP	Propyl 4-hydroxybenzoate	$C_{10}H_{12}O_3$	94-13-3	180.08	529	2.98
BuP	Butyl 4-hydroxybenzoate	$C_{11}H_{14}O_3$	94-26-8	194.23	159	3.47
HeP	Heptyl 4-hydroxybenzoate	$C_{14}H_{20}O_3$	1085-12-7	236.30	8.00	4.94
BzP	Benzyl 4-hydroxybenzoate	$C_{14}H_{12}O_3$	94-18-8	228.24	108	3.70
p-HB	4-hydroxybenzoate	$C_7H_6O_3$	99-96-7	138.12	14,500	1.39
BTR	1H-Benzotriazole	$C_6H_5N_3$	95-14-7	119.12	5960	1.17
TTR[c]	4/5-Methyl-1H-benzotriazole	$C_7H_7N_3$	29385-43-1	133.16	3070	1.71
XTR	5,6-Dimethyl-1H-benzotriazole	$C_8H_9N_3$	4184-79-6	147.18	914	2.26
1-OH-BTR	1H-Benzotriazol-1-ol	$C_6H_5N_3O$	2592-95-2	135.12	70,700	0.11
5-Cl-BTR	5-Chloro-1H-benzotriazole	$C_6H_4ClN_3$	94-97-3	153.57	2080	1.81
BTH	1,3-Benzothiazole	C_7H_5NS	128366-28-9	135.19	1680	2.17
2-OH-BTH	1,3-Benzothiazol-2-ol	C_7H_5NOS	934-34-9	151.19	2350	2.35
2- NH_2-BTH	1,3-Benzothiazol-2-amine	$C_7H_6N_2S$	136-95-8	150.20	1480	2.00
2-Me-S-BTH	2-(Methylsulfanyl)-1,3-benzothiazole	$C_8H_7NS_2$	615-22-5	181.28	111	3.22

[a] Data (at 25 °C, mg/L) cited from chemspider.com, which is estimate from Log K_{ow} (WSKOW v1.41).
[b] Predicted data cited from chemspider.com, which is generated using the US Environmental Protection Agency's EPISuite™, (KOWWIN v1.67 estimate).
[c] The mixture of isomers 4-Me-1-H-BTR and 5- Me-1-H-BTR, i.e. tolyltriazole (TTR), was considered as a target BTR compound in this study.